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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/536,552	03/28/00	MASON A	9926-003-999

020583
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1155 AVENUE OF THE AMERICAS
NEW YORK NY 10036-2711

HM22/1025

EXAMINER	
EPPS, J	
ART UNIT	**PAPER NUMBER**
1635	6

DATE MAILED: 10/25/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

1- File Copy

PTO-90C (Rev. 2/95)

U.S. G.P.O. 2000 ; 465-188/25266

Office Action Summary

Application No.	Applicant(s)
09/536,552	MASON et al
Examiner	**Group Art Unit**
Janet Epps	1635

[X] Responsive to communication(s) filed on Mar 28, 2000

[ ] This action is **FINAL.**

[ ] Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

[X] Claim(s) 1-6 is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

[ ] Claim(s) _____ is/are allowed.

[X] Claim(s) 1-6 is/are rejected.

[ ] Claim(s) _____ is/are objected to.

[ ] Claims _____ are subject to restriction or election requirement.

Application Papers

[ ] See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

[ ] The drawing(s) filed on _____ is/are objected to by the Examiner.

[ ] The proposed drawing correction, filed on _____ is [ ] approved [ ] disapproved.

[ ] The specification is objected to by the Examiner.

[ ] The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

[ ] Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

[ ] All [ ] Some* [X] None of the CERTIFIED copies of the priority documents have been

[ ] received.

[ ] received in Application No. (Series Code/Serial Number) _____.

[ ] received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

[ ] Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

[X] Notice of References Cited, PTO-892

[X] Information Disclosure Statement(s), PTO-1449, Paper No(s). 5

[ ] Interview Summary, PTO-413

[ ] Notice of Draftsperson's Patent Drawing Review, PTO-948

[ ] Notice of Informal Patent Application, PTO-152

— SEE OFFICE ACTION ON THE FOLLOWING PAGES —

DETAILED ACTION

Priority

1. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification (37 CFR 1.78).

Sequence Information

2. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. The applicant did not submit a CRF with this application.

A complete response requires that Applicants comply with the sequence rules, 37 CFR 1.821 - 1.825. Direct the reply to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply with the reply.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-6 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 , 3-5, and those claims dependent therefrom, recite abbreviations without providing a clear definition at the first instance of these terms.

Claim 1 recites the limitation "IAH", there is lack of antecedent basis for this limitation in the specification as filed, it is likely that Applicants intended this claim to recite the term "AIH" instead.

5. Claim 1 recites the limitations: "the step", "the presence", and "the disorder", there is lack of antecedent basis for these limitations in this claim.

6. Claim 2 recites the limitation "the nucleotide sequence" in claim 1. There is insufficient antecedent basis for this limitation in the claim.

7. Claim 4 recites the limitations "the step", "the presence", and "the virus". There is insufficient antecedent basis for these limitations in this claim.

8. Claim 5 recites the limitation "the virus", and "the PSC pol sequence", there is lack of antecedent basis for these limitations in this claim.

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1, and 3-6 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1, and 3-6 read on an isolated PSC associated retrovirus, a method for identifying a PSC associated retrovirus and a method for inhibiting replication of a PSC associated retrovirus.

Structural features that could distinguish a PSC associated retrovirus in the claimed genus from other retroviruses are missing from the disclosure. No common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the sequences of SEQ ID NO:1-7, alone is not sufficient to describe claimed genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, applicant was not in possession of the claimed genus.

11. Claims 5-6 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 5-6 read on a method for inhibiting replication of a PSC associated retrovirus in an individual infected with the virus by administering a composition which targets the PSC pol sequence in a therapeutically effective amount, and wherein the composition is an antisense molecule. The use of the phrase "therapeutically effective", in this context suggest that inhibiting the replication of a PSC associated retrovirus by the claimed method would produce a therapeutic effect in a patient having primary sclerosing cholangitis (PSC).

The method of use referred to in these claims implies *in vivo* applicability for enablement purposes. The applicant has only provided *in vitro* data describing the detection of viral nucleic acid in bile samples. There are no working examples either *in vivo* or *in vitro* demonstrating the efficacy of the claimed methods, wherein applicants administered a composition which targets the PSC pol sequence, particularly a composition comprising an antisense molecule, and the replication of a PSC associated retrovirus was inhibited. Furthermore, there are numerous factors which complicate nucleic acid based therapies which have not been shown to be overcome by routine experimentation. These include, the fate of the nucleic acid itself once administered to an individual (volume of distribution, and rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of nucleic acid taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the nucleic acid, and the stability of the nucleic acid.

Furthermore, it is well established in the art that there is a significant level of unpredictability regarding the behavior of nucleic acid base therapeutics. According to Crooke (1998), "extrapolations from in vitro uptake studies to predictions about *in vivo* pharmacokinetic behavior are entirely inappropriate". Crooke also teaches that variations in cellular uptake and

distribution of oligonucleotides are influenced by a variety of factors: length of oligonucleotide, modifications, sequence of oligonucleotide and cell type. Moreover, Crooke clearly teaches that there is a significant level of factors which influence the behavior of nucleic acid based compounds thereby rendering the activity of nucleic acid based therapeutics unpredictable, and thus much experimentation is required to screen multiple nucleic acid compounds to determine not only their efficacy *in vitro* but also *in vivo.*

Therefore, the specification as filed does not describe the claimed method, in a sufficient manner so as to enable one of ordinary skill in the art to practice the present invention without undue experimentation. These conclusions are based upon the known unpredictability regarding the behavior of nucleic acid based compounds *in vivo* and further with the production of desired secondary effects, such as regulating a condition associated with the expression of a viral gene, and the lack of guidance in the specification as filed in this regard.

The quantity of experimentation required to practice the invention as claimed would require determining the modes of delivery in an individual *in vivo* such that a sufficient amount of a composition which targets the PSC pol sequence in a PSC associated virus is supplied in a sufficient concentration and for a sufficient period of time, such that viral replication is inhibited and the desired secondary effects are obtained. The specification as filed provides no specific guidelines in this regard. The deficiencies in the specification would constitute undue experimentation since these steps must be achieved without instructions from the specification before one is enabled to practice the claimed invention.

Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over Mason et al. in view of Peterson et al.

According to Mason et al. retroviruses have been implicated in the aetiology of various autoimmune diseases. They used immunoblots as a surrogate test to find out whether retroviruses play a part in the development of primary biliary cirrhosis. Mason et al. discovered that HIV-1 p24 gag seroreactivity was found in 27 (35%) of 77 patients with primary biliary cirrhosis, 14 (29%) of 48 patients with systemic lupus erythematosus, 14 (50%) of 28 patients with chronic viral hepatitis, and nine (39%) of 23 patients with either primary sclerosing cholangitis or biliary atresia (See entire document, especially p. 1620) .

The Mason et al. reference does not teach a method for detecting the presence or absence of a the nucleic acid molecule of a virus associated with PSC in their method for identifying an individual having PSC, IAH, Crohn's disease or ulcerative colitis.

Peterson et al. teach a method for detection of HIV by oligonucleotide hybridization (See entire document; especially col. 15, line 1-66 through col. 19, lines 1-50). This reference discloses oligonucleotides targeted to HIV nucleic acids can be used as detection probes to measure the presence of a HIV target sequence and as amplification primers to selectively amplify

HIV nucleic acid. Hybridization to either the target nucleic acid or a nucleotide sequence region complementary to the target sequence is useful for detecting the presence of HIV.

Neither reference provides a direct teaching of a method for identifying an individual having PSC, IAH (or AIH), Crohn's disease or ulcerative colitis, comprising the step of detecting the presence or absence of a PSC associated retroviral nucleic acid. However, it would have been obvious to one of ordinary skill in the art to modify the teachings of Mason et al. with the teachings of Peterson et al. in the design of the method of the instant invention because Peterson et al. clearly teach a method for detection of HIV, and Mason et al. provides a direct link between the presence of PSC in an individual and HIV-1 infection. Therefore, one having ordinary skill in the art would have been motivated to combine the teachings of Mason et al. and Peterson et al. in the formulation of the method of the instant invention, because assaying the presence or absence of HIV-1 retroviral nucleic acid in a patient would be functionally equivalent to assaying the presence or absence of PSC in an individual as taught by Mason et al.

Therefore the invention as a whole is *prima facie* obvious over Mason et al. in view of Peterson et al.

Claim Rejections - 35 USC § 102

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

15. Claims 3-4 are rejected under 35 U.S.C. 102(e) as being Peterson et al. as evidence by Mason et al.

Peterson et al. disclose a method for the detection of HIV nucleic acid as discussed above. Furthermore, Peterson et al. describe compositions comprising the HIV virus (See entire document; especially col. 15, line 1-66 through col. 19, lines 1-50). According to Mason et al. HIV-1 is a PSC associated retrovirus. Therefore, Peterson et al. disclose compositions comprising a PSC associated retrovirus and a method for detecting the presence of a PSC associated virus in an individual comprising identifying the presence or absence of nucleic acid molecules associated with the HIV retroviral genome.

Peterson et al. teach each and every aspect of the instant invention, thereby anticipating applicant's claimed invention, as evidenced by Mason et al.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps whose telephone number is (703) 308-8883. The examiner can normally be reached on Monday through Friday from 8:30 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, George Elliott, can be reached at (703) 308-4003. The fax number for this group is (703) 305-7939.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Janet L. Epps, Ph.D.

ROBERT A. SCHWARTZMAN
PRIMARY EXAMINER

October 23, 2000

Application No.:09/536,552

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

- [X] 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to these regulations, published at 1114 OG 29, May 15, 1990 and at 55 FR 18230, May 1, 1990.
- [X] 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).
- [X] 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).
- [ ] 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."
- [ ] 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).
- [ ] 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).
- [ ] 7. Other: _____

Applicant Must Provide:

- [X] An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".
- [X] An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.
- [X] A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216
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